

WHAT IS CLAIMED IS:

Sub A1  
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1. A method for determining a subject's predisposition to early-onset menopause, comprising detecting at least one allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2, or an allele in linkage disequilibrium with any of the above, wherein detection of said at least one allele is predictive of the subject's predisposition to early-onset menopause.

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2. A method of claim 1, wherein said at least one allele is in linkage disequilibrium with IL-1RN (+2018) allele 2.

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3. A method of claim 1 wherein said at least one allele is selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; and IL-1A (+4845) allele 1.

4. A method of claim 3, wherein said at least one allele is IL-1RN (+2018) allele 2.

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5. The method of any of claims 1-4 wherein detecting said at least one allele comprises allele specific oligonucleotide hybridization.

6. The method of any of claims 1-4, wherein detecting said at least one allele comprises RFLP analysis.

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7. The method as in claims 1-4, wherein detecting said at least one allele comprises amplification of a nucleic acid.

8. The method of claim 7, wherein said amplification further comprises PCR.

9. The method of claim 7, wherein said amplification comprises using a first oligonucleotide that overlaps a second oligonucleotide, or a complement thereof, selected from the group consisting of:

5' CTC AGC AAC ACT CCT AT 3' (SEQ ID No. 5);  
5' TCC TGG TCT GCA GGT AA 3' (SEQ ID No.6);  
5' CTA TCT GAG GAA CAA CCA ACT AGT AGC 3' (SEQ ID No.7);  
5' TAG GAC ATT GCA CCT AGG GTT TGT 3' (SEQ ID No.8);  
5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No.9);  
5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No.10);  
5' AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID No.11);  
5' TTA CAT ATG AGC CTT CCA TG 3' (SEQ ID No.12);  
5' TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID No.13);  
5' GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID No.14);  
5' ATG GTT TTA GAA ATC ATC AAG CCT AGG GCA 3' (SEQ ID No.15);  
5' AAT GAA AGG AGG GGA GGA TGA CAG AAA TGT 3' (SEQ ID No.16);  
5' TTACGCAGATAAGAACCAGTTTGG 3' (SEQ ID No.17);  
5' TTCTCTGGACGCTTGCTCACCAG 3' (SEQ ID No.18);  
5' ATGTATAGAATTCCATTCCTG 3' (SEQ ID No.19);  
5' TAAATCAAGTGTGATGTAG 3' (SEQ ID No.20);  
5' GGGATTACAGGCGTGAGCCACCGCG 3' (SEQ ID No.21);  
5' TTAGTATTGCTGGTAGTATTCATAT 3' (SEQ ID No.22);  
5' GAGGCGTGAGAATCTCAAGA 3' (SEQ ID No.23);  
5' GTGTCCTCAAGTGGATCTGG 3' (SEQ ID No.24);  
5' GGGCAACAGAGCAATGTTTCT 3' (SEQ ID No.25); and  
5' CAGTGTGTGAGTGTACTGTT 3' (SEQ ID No.26).

10. The method of claim 9, wherein said first oligonucleotide comprises at least ten nucleotides of said second oligonucleotide.

11. A method for determining a subject's susceptibility to early-onset menopause comprising:

obtaining a nucleic acid sample from said subject; and,

genotyping said nucleic acid;

wherein detecting an allelic pattern from an IL-1 haplotype associated with early-onset menopause indicates an increased susceptibility to early-onset menopause.

12. The method of claim 11, wherein said haplotype associated with early-onset menopause comprises an allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

13. A kit for determining a woman's predisposition to early-onset menopause comprising a first primer that hybridizes 5' or 3' to a marker of an IL-1-related gene associated with early-onset menopause, wherein said kit is used to detect a predisposition to early-onset menopause.

14. The kit of claim 13, wherein said marker is selected from the group consisting of: IL-1RN (+2018); IL-1RN (VNTR); IL-1A (222/223); IL-1A (gz5/gz6); IL-1A (-889); IL-1B (+3954); IL-1B (-511); gaat.p33330; Y31; IL-1RN exon 1ic (1812); IL-1RN exon 1ic (1868); IL-1RN exon 1ic (1887); Pic (1731); IL-1A (+4845); IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

15. The kit as of claim 14, further comprising a second primer that hybridizes 3' to said marker when said first primer hybridizes 5' and hybridizes 5' to said marker when said first primer hybridizes 3'.

16. The kit of claim 15, wherein said first primer and said second primer hybridize to a region that includes said marker, wherein said region is in the range of between about 50 and 1000 base pairs.

17. The kit of claim 15, wherein said primers are selected from the group consisting of:

5' CTC AGC AAC ACT CCT AT 3' (SEQ ID No. 5);

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5' TCC TGG TCT GCA GGT AA 3' (SEQ ID No.6);  
5' CTA TCT GAG GAA CAA CCA ACT AGT AGC 3' (SEQ ID No.7);  
5' TAG GAC ATT GCA CCT AGG GTT TGT 3' (SEQ ID No.8);  
5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No.9);  
5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No.10);  
5' AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID No.11);  
5' TTA CAT ATG AGC CTT CCA TG 3' (SEQ ID No.12);  
5' TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID No.13);  
5' GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID No.14);  
5' ATG GTT TTA GAA ATC ATC AAG CCT AGG GCA 3' (SEQ ID No.15);  
5' AAT GAA AGG AGG GGA GGA TGA CAG AAA TGT 3' (SEQ ID No.16);  
5' TTACGCAGATAAGAACCAGTTTGG 3' (SEQ ID No.17);  
5' TTTCCTGGACGCTTGCTCACCAG 3' (SEQ ID No.18);  
5' ATGTATAGAATTCATTCCTG 3' (SEQ ID No.19);  
5' TAAAATCAAGTGTGATGTAG 3' (SEQ ID No.20);  
5' GGGATTACAGGCGTGAGCCACCGCG 3' (SEQ ID No.21);  
5' TTAGTATTGCTGGTAGTATTCATAT 3' (SEQ ID No.22);  
5' GAGGCGTGAGAATCTCAAGA 3' (SEQ ID No.23);  
5' GTGTCCTCAAGTGGATCTGG 3' (SEQ ID No.24);  
5' GGGCAACAGAGCAATGTTTCT 3' (SEQ ID No.25); and  
5' CAGTGTGTCAGTGTACTGTT 3' (SEQ ID No.26).

18. The kit of claim 14, further comprising a DNA sampling means.

19. The kit of claim 14, further comprising a control.

20. The kit of claim 14, further comprising a DNA detection means.

21. The kit of claim 15, wherein said first primer and/or said second primer further comprises a detectable label.

22. A method of identifying an allelic pattern associated with early-onset menopause, said method comprising identifying a first allelic pattern that is in linkage disequilibrium with a second allelic pattern associated with early-onset menopause, wherein said first allelic pattern is associated with early-onset menopause.

23. The method of claim 22, wherein said first allelic pattern comprises alleles at a single polymorphic region within the IL-1 gene loci.

24. The method of claim 23, wherein said second allelic pattern is selected from the group consisting of IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

25. A transgenic non-human animal which contains and expresses an IL-1 allele that is associated with early onset of menopause in humans.

26. A transgenic animal of claim 25, wherein said allele is IL-1RN (+2018) allele 2.

27. A method for identifying an EOM-associated biomarker comprising:

observing at least one biomarker in a subject having an EOM associated allele;  
and

observing at least one biomarker in a subject not having an EOM associated allele,  
wherein, a difference in at least one biomarker between the subjects indicates that the biomarker is an EOM-associated biomarker.

28. A method of claim 27 wherein said observations are performed at different times during the progression of the subjects towards and/or through menopause.

29. A method of claim 27 wherein said EOM associated allele is IL-1RN (+2018) allele 2.

30. A method for identifying an EOM biomarker comprising:

observing at least one biomarker in a cell having an EOM associated allele; and

observing at least one biomarker in a cell not having an EOM associated allele,

wherein, a difference in a biomarker in the subjects indicates that the biomarker is an EOM biomarker.

31. A method of claim 30 wherein said EOM associated allele is IL-1RN (+2018) allele 2.

32. A method for screening test substances to identify an EOM therapeutic, said method comprising:

contacting a subject with a test substance; and

observing at least one biomarker in said subject, wherein a change in a biomarker from an EOM-associated phenotype to a non-EOM-associated phenotype identifies a test substance that is likely to be effective as an EOM therapeutic.

33. A method of claim 32 wherein said biomarker is an IL-1 bioactivity.

34. A method of claim 32 wherein said subject is a transgenic animal of claim 25.

35. A method of claim 32 wherein said test substance is a nutraceutical.

36. A method for screening test substances to identify an EOM therapeutic, said method comprising:

contacting a cell containing DNA comprised of at least one allele of an IL-1

(44112332) haplotype with a test substance; and

observing at least one biomarker in said cell,

wherein a change in a biomarker from an EOM-associated phenotype to a non-EOM-associated phenotype identifies a test substance that is likely to be effective as an EOM therapeutic.

37. A method of claim 36 wherein said biomarker is an IL-1 bioactivity.

38. A method of claim 36 wherein said allele is IL-1RN (+2018) allele 2.

39. A method of claim 36 wherein said test substance is a nucleic acid.

40. A method of claim 36 wherein said test substance is a nutraceutical.

41. A method of postponing, preventing or ameliorating EOM, comprising contacting a subject with an effective amount of an EOM therapeutic identified by a method of claim 32 or 36.

42. A method of claim 41, wherein said EOM therapeutic is a nutraceutical.

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